Applicants gratefully acknowledge the personal interview granted by the Examiner to applicants' counsel on December 20, 2001. During the interview, applicants' counsel proposed claim amendments to clarify the inventive subject matter and thereby overcome the rejections under 35 U.S.C. § 112, first and second paragraphs. The Examiner indicated that the claim amendments may overcome the rejections. The claim amendments proposed during the interview are now presented herein.

Applicants also gratefully acknowledge the Examiner's indication in the Office Action that claim 22 is allowable. Claims 1-21 have been rejected in the Office Action. Claims 1, 16, 18 and 21 are amended herein, and claims 23-28 are added herein, to clarify the subject matter of the invention. Claims 1-28 are now pending in this matter.

Basis for the claim amendments and newly added claims is found throughout the specification and specifically at pages 1, 2 and 21. No new matter is submitted by these claim amendments or newly added claims. Further, no new issues are raised by the claim amendments or newly added claims. Accordingly, applicants respectfully submit that the claim amendments and newly added claims should be entered after final in accordance with MPEP 714.13 because they adopt suggestions of the Examiner and/or remove issues for appeal.

REJECTION UNDER 35 U.S.C. § 112 SECOND PARAGRAPH

Claims 1-21 are rejected under 35 U.S.C. § 112, second paragraph, as indefinite for several reasons discussed in detail below. Applicants submit that the claims prior to their amendment herein were definite because persons skilled in the art would have been readily able to ascertain the scope of the claimed invention. Nonetheless, Applicants amended their claims substantially as suggested by the Examiner, in an effort to expedite prosecution of the application. The amendments are intended to merely add consistency to certain portions of the claims, and they are not related to patentability of the claims. The amended claims continue to satisfy the definiteness requirements of 35 U.S.C. § 112, second paragraph.

With regard to claims 1, 16 and 21, the phrase: "a range of promoter activities which is within a range from the weakest possible activity that is detectable to the strongest possible activity that is detectable" is objected to as being vague and indefinite. Applicants have

amended each of these claims to replace that phrase with the phrase "a range of promoter activities which is within a range from the weakest activity that is detectable by inserting each of the set of promoters into a vector comprising a promoterless β-galactosidase reporter gene system, transforming a host strain with the resulting vector and cultivating the transformed host strain with the resulting vector and cultivating the transformed host strain to express β-galactosidase from the reporter gene and identifying that promoter set showing the weakest β-galactosidase activity, to the strongest activity that is detectable by the same procedure with the exception that the promoter of the promoter set showing the strongest activity in said reporter gene system is identified."

With regard to claim 1, the phrase "at least two consensus sequences corresponding to conserved sequences identified in said organism or group of organisms" is objected to as also being vague and indefinite. Claim 1 has been amended to replace the objected to phrase with the phrase "the at least two consensus sequences, when the selected organism or group of organisms is prokaryotic, being selected from the group consisting of TATAAT, TATRAT, TTGACA and an activator binding site upstream of the TATAAT sequence (a UAS) and the at least two consensus sequences, when the selected organism or group of organisms is eukaryotic, being selected from the group consisting of a TATA-box and a UAS upstream of said TATA-box."

With regard to claims 1 and 16, the phrase "substantially random" is objected to. The term "substantially" has been deleted

With regard to claim 18, the phrases "a desired range of promoter activities" and "optimal level of gene expression" are objected to. These phrases have been replaced with the phrases "controlling in an organism the flux of a cellular metabolite or the expression of a desired gene product, said method comprising at least one step of changing the expression level of at least one gene in the pathway leading to formation of said metabolite or the expression level of said desired gene product" and "where the at least one gene in the pathway or the gene expressing the desired gene product is under the control of its native promoter, a higher or a lower flux of the cellular metabolite or a higher or a lower expression of the desired gene product."

REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claims 1-21 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

At the outset, applicants respectfully point out that the initial burden of establishing a basis for denying patentability of a claimed invention rests upon the Patent Office. *See In re Fine*, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988). It is equally well established that the Patent Office bears the initial burden to establish a reasonable basis to question the written description provided in the specification for the invention defined in Applicants' claims. *See In re Wright*, 27 U.S.P.Q.2d 1510 (Fed. Cir. 1993).

Applicants respectfully traverse the Examiner's rejection for the following reasons. In summary, applicants' full scope of claimed subject matter was described in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention, prior to the amendment of the claims herein. Nonetheless, in the interest of advancing prosecution, applicants amended their claims. Applicants' claimed subject matter continues to be described in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

It is well established that a disclosure of the specification provides a description of the claimed subject matter if it reasonably conveys to persons skilled in the art that the inventor has possession of that subject matter at the time the application was filed. *See, e.g., Fujikawa v. Wattanasin*, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996) and *Vas-Cath, Inc.v. Mahurkar*, 19 U.S.P.Q.2d 1111 (Fed. Cir. 1991). Applicants respectfully submit that their specification, as filed, satisfied that standard because persons of ordinary skill in the art, familiar with applicants' specification, would clearly understand that they possessed the claimed subject matter. This is indicated, for example, by the Examiner's appreciation of the full scope of Applicants' claimed invention in the Office Action.

Further, the new Written Description Guidelines specify that one of the factors to be considered in determining if the written description requirement is satisfied is whether a representative number of species is disclosed in the specification. (See Guidelines, page 9). A

representative number of species is disclosed if one skilled in the art would recognize that applicant possessed the necessary common attributes or features of the elements of the members of the genus in view of the species disclosed and claimed. *Id.*

As clearly demonstrated by a review of the specification, and contrary to the Examiner's assertion, applicants do indeed disclose such a representative number of species. For instance, Examples 1 and 2 on pages 17 to 27 of the specification specifically provide a set of promoter sequences for *L. lactis*, and Example 7 on pages 31-34 of the specification specifically provide a set of promoter sequences for *Saccharomyces cerevisiae*. Further examples are provided concerning other bacteria, such as *Bacillus subtilis, Pseudomonas* and *E. coli*, and various exemplary methodologies for constructing the promoter sequences in accordance with the claimed invention, as well.

Moreover, the adequacy of the specification is further underscored by the fact that the claims, as amended, now recite that the set of promoter sequences covers with respect to promoter strength "a range of promoter activities which is within a range from the weakest activity that is detectable by inserting each of the set of promoters into a vector comprising a promoterless β-galactosidase reporter gene system, transforming a host strain with the resulting vector and cultivating the transformed host strain with the resulting vector and cultivating the transformed host strain to express β-galactosidase from the reporter gene and identifying that promoter set showing the weakest β-galactosidase activity, to the strongest activity that is detectable by the same procedure with the exception that the promoter of the promoter set showing the strongest activity in said reporter gene system is identified." The methodology for determining β-galactosidase activity is provided in the specification on page 21 providing further evidence that applicants had possession of the claimed subject matter at the time the application was filed.

Additionally, this amendment also renders moot the Examiner's assertion that the claimed invention is characterized by a set of promoters that must encompass both the weakest and strongest levels of gene expression for <u>any</u> given gene under <u>any</u> given conditions and measured by <u>any</u> assay capable of determining gene expression levels. For the sole purpose of clarifying the invention, the conditions, assays, etc. which were provided in the specification are

now recited in the claims. Therefore, one of skill in the art would reasonably conclude applicants were in possession of the claimed invention.

REQUEST FOR ALLOWANCE

For at least the reasons detailed above, the applicants respectively submit that all of the claims in the application are patentable. Favorable consideration, entry of this amendment, and issuance of a notice of allowance are respectively requested.

In the event any issues remain, the Examiner is encouraged to contact applicants' representatives to resolve such issues in an expeditious manner, and place the application in condition for allowance.

In the event any fees are incurred upon the filing of these documents, please charge the undersigned's Deposit Account No. 50-0206.

Respectfully submitted,

HUNTON & WILLIAMS

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APPENDIX

1. (Twice Amended) A set of promoter sequences suitable for optimizing the expression of a gene in a selected organism or group of organisms, said set of promoter sequences covering, with respect to promoter strength for said gene, a range of promoter activities which is within a range from the weakest [possible] activity that is detectable by inserting each of the set of promoters into a vector comprising a promoterless β-galactosidase reporter gene system, transforming a host strain with the resulting vector and cultivating the transformed host strain with the resulting vector and cultivating the transformed host strain to express β-galactosidase from the reporter gene and identifying that promoter set showing the weakest β-galactosidase activity, to the strongest [possible] activity that is detectable by the same procedure with the exception that the promoter of the promoter set showing the strongest activity in said reporter gene system is identified, each promoter sequence of said set of promoter sequences comprising a double stranded DNA sequence, the sense strands of which comprise

at least two consensus sequences, said at least two consensus sequences corresponding to conserved sequences identified in said organism or group of organisms, at least half of each of said consensus sequences being kept constant in the set of promoter sequences, the at least two consensus sequences, when the selected organism or group of organisms is prokaryotic, being selected from the group consisting of TATAAT, TATRAT, TTGACA and an activator binding site upstream of the TATAAT sequence (a UAS) and the at least two consensus sequences, when the selected organism or group of organisms is eukaryotic, being selected from the group consisting of a TATA-box and a UAS upstream of said TATA-box and, between said consensus sequences or flanking at least one of said consensus sequences, at least one nucleotide spacer sequence, at least part of which, relative to the corresponding spacer sequence of the identified promoter, is varied by [substantially] random incorporation of nucleotides that are selected from the group consisting of the nucleobases A, T, C and G,

the set of promoter sequences covering the range of promoter activities for said gene, in steps, each step changing the activity by 50-100%.

16. (Twice Amended) A method of constructing a set of promoter sequences which is suitable for optimizing the expression of a gene in a selected organism or group of organisms, the method comprising the steps of

(i) identifying in said organism or group of organisms a promoter sequence comprising at least two consensus sequences, which consensus sequences correspond to conserved sequences identified in said organism or group of organisms, at least one of the consensus sequences being flanked by a non-conserved nucleotide spacer sequence or both or said consensus sequences being separated by the non-conserved nucleotide spacer sequence,

(ii) constructing a set of single stranded DNA sequences comprising at least half of each of the consensus sequences, and a non-conserved nucleotide spacer sequence, at least part of which is varied by a [substantially] random incorporation of nucleotides selected from the group consisting of the nucleobases A, T, C and G, whilst keeping the at least half of the consensus sequences constant, and

(iii) converting the single stranded DNA sequences into double stranded DNA sequences to obtain the set of promoter sequences covering, with respect to promoter strength, a range of promoter activities which is within a range from the weakest [possible] activity that is detectable by inserting each of the set of promoters into a vector comprising a promoterless β-galactosidase reporter gene system, transforming a host strain with the resulting vector and cultivating the transformed host strain with the resulting vector and cultivating the transformed host strain to express β-galactosidase from the reporter gene and identifying that promoter set showing the weakest β-galactosidase activity, to the strongest [possibly] activity that is detectable by the same procedure with the exception that the promoter of the promoter set showing the strongest activity in said reporter gene system is identified.

18. (Thrice Amended) A method of controlling in an organism the flux of a cellular metabolite or the expression of a desired gene product, said method comprising at least one step of changing the expression level of at least one gene in the pathway leading to formation of said metabolite or the expression level of said desired gene product, [optimizing the expression of a gene in an organism], the [method] step comprising

(i) selecting from the set of promoter sequences of claim 1 a plurality of promoter sequences covering a desired range of promoter activities,

(ii) transforming said set of promoter sequences into cells of the organism, placing in each of said cells the gene to be expressed under the control of at least one promoter of the set,

(iii) cultivating the transformed cells to obtain clones thereof and selecting among said clones a clone having, relative to an otherwise identical clone where the at least one gene in the pathway or the gene expressing the desired gene product is under the control of its native promoter, a higher or a lower flux of the cellular metabolite or a higher or a lower expression of the desired gene product [showing an optimal level of gene expression].

21. (Thrice Amended) A method of isolating a promoter sequence being capable of optimizing the expression of a gene in a selected organism, the method comprising

(i) constructing, using the method of claim 16, a set of promoters covering, with respect to promoter strength, a range of promoter activities which is within a range from the weakest [possible] activity that is detectable by inserting each of the set of promoters into a vector comprising a promoterless β-galactosidase reporter gene system, transforming a host strain with the resulting vector and cultivating the transformed host strain with the resulting vector and cultivating the transformed host strain to express β-galactosidase from the reporter gene and identifying that promoter set showing the weakest β-galactosidase activity, to the strongest [possible] activity that is detectable by the same procedure with the exception that the promoter of the promoter set showing the strongest activity in said reporter gene system is identified,

(ii) transforming said set of promoters into cells of the selected organism, placing in each of said cells the gene to be expressed under the control of at least one promoter of the set,

(iii) cultivating the transformed cells to obtain clones thereof and selecting among said clones a clone having, relative to an otherwise identical clone where the at least one gene in the pathway or the gene expressing the desired gene product is under the control of its native promoter, a higher or a lower flux of the cellular metabolite or a higher or a lower expression of the desired gene product [showing optimal level of gene expression], and

(iv) isolating said promoter sequence from the clone [showing optimal level of gene expression].